A STUDY ON PREVALENCE OF SILENT MYOCARDIAL ISCHEMIA IN NEWLY DETECTED TYPE-2 DIABETES AND ALSO IN KNOWN DIABETES OF VARIOUS DURATION

Submitted to

The Tamilnadu Dr. M.G.R. Medical University

FOR
M.D. DEGREE EXAMINATION
BRANCH – I (GENERAL MEDICINE)

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
CHENNAI, INDIA

MARCH 2008

CERTIFICATE

Certified that the dissertation entitled **"A STUDY ON PREVALENCE OF SILENT MYOCARDIAL ISCHEMIA IN NEWLY DETECTED TYPE-2 DIABETES AND ALSO IN KNOWN DIABETES OF VARIOUS DURATION"** is a bonafide work done by **Dr. A. MOHAMED KALIFA,** Postgraduate Student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of the regulation of the Tamil Nadu **Dr. M.G.R Medical University** for the award of **M.D. Degree, Branch – I, Part II (General Medicine)** during the academic period of May 2005 to March 2008.

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ACKNOWLEDGEMENT

I owe my sincere thanks to the Dean, Government Kilpauk Medical College and Hospital, Chennai-10, **Prof. Dr. DHANAPAL, M.D., D.M.,** for allowing me to avail the facilities needed for my dissertation work.

I am extremely grateful to **Prof. Dr. RAJENDRAN, M.D.,** Professor and Head of the Department of Medicine, Government. Kilpauk Medical College and Hospital for permitting me to do the study and for his constant encouragement and guidance.

I express my gratitude to my eminent teachers **Prof. SELVAM, M.D., Prof. A. JOSEPH NAVASEELAN, M.D., Prof. CHINNAIYAN, M.D.,** and **Prof. CHELLAM, M.D.,** for their expert guidance.

I am also thankful to our Registrar **Dr. GOBINATHAN, M.D., D.M.,** and to my Assistant Professors **Dr. KULOTHUNGAN, M.D., Dr. MALAR VIZHI, M.D.,** for their constant encouragement.

I express my gratitude to **Prof. Dr. ANAND MOSES, M.D.,** Dr. Ambedkar Institute of Diabetology, Government Kilpauk Medical College and Hospital for his expert guidance and constant encouragement. I also thank all Assistant Professors of Diabetology for their constant encouragement.

I express my gratitude to **Dr. MANOKARAN, M.D.,** Department of Cardiology, Kilpauk Medical College and Hospital for his guidance and encouragement. I also thank all Assistant Professors, Department of Cardiology for their constant encouragement.

Last, but not the least, my sincere thanks to all the patients who cooperated for this study, without whom this study could not have been undertaken.

CONTENTS

INTRODUCTION

It is astonishing that Indians are aware of diabetes and its complication since 1500 BC. Charaka samhita, sushruta samhita and Astanga hrdaya are together called vridhatrayi or triad of ancients. This text deals with aetiology, symptomatology, pathology, prognosis, complications and principles of treatment and management of eight major diseases including **prameha.** The literary meaning of *Prameha* is *'Pra'* means excess, *'Meha'* means urine. It has been classified into 20 types under which *madhumeha* (Diabetes Mellitus) is one of the classification, which means *Madhu*-honey and *meha*-urine, in *Charaka samhita*[1]*.*

World wide, there is a Vast potential for Diabetes associated cardio-vascular disease, notably among the 33 million people in India (in 2003) and 23 million in China estimated to have Diabetes, predominantly type2. Many regions now have Diabetes prevalence of > 10 %.[2]

CAD is more frequent, more severe, more extensive and more diffuse in Diabetes as compared to Non-Diabetic. In the Framingham study, the incidence of IHD in Diabetes was approximately twice that of Non-Diabetic.[3] ***Jacoby and Nesto***[4] reported that over all prevalence of CAD was as great as 55 %

among adults with Diabetes as compared with 2-4 % for general population. In India the prevalence of Heart disease is escalating.

We, ***Indians*** who have highest number of Diabetic population in the world is at constant threat from the CAD which is more common in Diabetic population. ***Thus India faces the dangerous dual epidemic of Diabetes and CAD.***

Since CAD is more common and fatal in Diabetics than in Non-Diabetics, the treating physician should aim at primary prevention of IHD in Diabetics and treatment of risk factors, such as Dyslipidemia, obesity, Hypertension, Smoking, Insulin resistance. Recently we have realized in terms of Plasma Cholesterol, Triglycerides as well as blood pressure value should be different in Diabetic and Non-Diabetic subjects. In addition to the treatment of risk factors should be accompanied by a systemic search for silent disease markers such as silent myocardial ischemia which is 2-3 times more frequent among Diabetics and thus CAD can be prevented before a significant clinical event.

AIM OF THE STUDY

1. To study the prevalence of Silent Myocardial Ischemia in newly detected type 2 diabetes mellitus and also already known type 2 diabetic patients of various duration using exercise stress test.

2. To study the impact of duration of diabetes in asymptomatic ischemic heart disease.

3. To study the association and influence of other risk factors causing coronary artery disease in diabetics.

REVIEW OF LITERATURE

HISTORY OF DIABETES IN INDIA

Diabetes in India has a long history since ancient time. The oldest reference of this disease dates back to more than 4500 years. The name of the disease found in '*Devik yuga'* tells it has been known and treated by Indians long ago. It has been mentioned (in *Chakradatta, Rasayana* chapter, *Sloga 195*) that Lord Shiva has dictated a formulation for the treatment of *prameha* to his son Lord Ganesha. Another view claims that Lord Ganesha was afflicted by *prameha* because of his eating and working habits like taking lots of sweets (*modaka*) and sitting in same place for which his father gave him the formulation named '*Siva gutika'* to rectify the disorder.[5]

EPIDEMIOLOGY OF DIABETES IN INDIA

Burden of Diabetes: Trend And Future Projections

The impact of the world wide explosion of type 2 diabetes mellitus (which accounts for approximately 85 to 95% of all cases of diabetes) will remain centered in the developing countries. Since by the year 2025, 75% of all the people with diabetes will be in the developing countries as compared with 62% in 1995. By 2025, there will be a 42 % increase from 51-72 million in the developed

countries and 170% increase from 84-228 million, in the developing countries.[6]

India already faces a grave problem with the largest number of subjects with diabetes (approximately 33 million in 2003) and it is expected to escalate further with the number increasing to 57.2 million in the year 2025 and by the year 2030 it may be 80.9 million.[7] The prevalence estimate by the international Diabetes Federation (IDF) reported the worldwide prevalence to be increasing from 5.1-6.3% (between 2003-2025).[8]

Epidemiology studies in India on diabetes were taken up following several reports showing that type 2 diabetes among migrant Asian Indian population in several countries was high compared with the host population and other migrant ethnic groups.[9] Irrespective of the differences in anthropometry, dietary and socioeconomic factors and migratory patterns- the migrant Indians showed a higher prevalence of type 2 diabetes than Europeans.[10]

Epidemiology study from Mauritius[11] also showed the prevalence of type 2 DM in migrant Indian is 18%. The rate of prevalence of type 2 diabetes in the migrant Indian population of Mauritius is similar to many of the urban rates of prevalence of diabetes in the mainland.

A series of studies from Chennai showed that the percentage of adult urban subjects affected had increased from 5.2% in 1984 to 8.2% in 1989, 11.6% in 1995 and 13.9% in 2000 which further increased to 14.3% in 2004[13]. A National Urban Survey in 2000 showed that the prevalence of diabetes in urban India was 12.1% in subjects aged > 20 years.[14]

The prevalence in all the cities was more than 9% (Varied from 9.3-16.6%). The prevalence in six major cities are Chennai-13.5%, Bangalore-12.4%, Hyderabad-16.6%, Kolkata-11.7%, New Delhi-11.6% and Mumbai-9.3%.[14]

CHORONIC COMPLICATIONS OF DIABETES

Long-standing diabetes mellitus is associated with an increased prevalence of microvascular and macrovascular diseases. Data from Chennai shows that the prevalence of complications of type 2 diabetes are as follows: Retinopathy 23.7%, nephropathy 5.5%, peripheral neuropathy 25.5%, CHD 11.4%, PVD 4.0% and stroke 0.9%. Prevalence of hypertension is also high (38.2%).[15]

EPIDEMILOGY OF DIABETES AND CAD – INDIAN SCENARIO

Indians also have three times higher risk of developing CAD compared to Chinese and are 20 times more likely to die due to CAD compared to native black or white South Africans.[16] The

SHARE study demonstrated that south Asians had higher prevalence of cardiovascular disease compared to Europeans and Chinese living in Canada.[17]

Moreover, Indians also tend to develop CAD two to three decades earlier compared to Europeans.[18] This predilection for CAD among Indians was reported fifty years ago which was confirmed later by several studies.[19,20]

In India approximately 2.78 million deaths are due to cardiovascular disease, of which over 50% is due to CAD, ***making CAD the number one killer disease in our country.***[21]

Prevalence of CAD in Indians has been shown to be escalating in alarming proportions in the last few decades. The prevalence of heart disease in 1950s was 1.05%; this increased to 9.7% in 1990 and to 11.0% in 2000 in urban population.[22-25] In the Jaipur Heart Watch-2 study conducted in 2002, prevalence of CAD was reported to be 8.2%.[26]

This rising trend in CAD will shortly make India, ***the leader in CAD death rates also.***[27] Thus India faces the ***dangerous dual epidemic of diabetes and CAD*** and in many respects, the aetiopathogenesis of both conditions may be similar.

PREVALENCE OF CAD IN DIABETES

In CUPS study, overall, 11% of the total population had CAD and the age-standardized prevalence (standardized to the 1991 census of Chennai) was 9.0%.[28]

Prevalence of CAD was higher among diabetic subjects (21.4%) (known diabetes 25.3% and newly diagnosed diabetes-13.1%) compared to 14.9% among subjects with impaired glucose tolerance (IGT) and 9.1% among subjects with normal glucose tolerance.[25]

Prevalence of known myocardial infarction was three times higher in subjects with diabetes compared those without. At every age point, subjects with diabetes and impaired glucose tolerance had higher prevalence of CAD compared subjects with normal glucose tolerance. ***The risk for CAD thus seems to increase even at the stage of impaired glucose tolerance.***

MORTALITY DUE TO CAD IN DIABETIC SUBJECTS

Mortality among diabetic subjects with CAD is higher than in non-diabetic subjects.[29] Studies have also shown that the myocardial infarction in diabetic subjects is more extensive and recurrence is more common in them compared to non-diabetic subjects. Furthermore, the prognosis after a clinical event is worse

in diabetic subjects compared to non-diabetic subjects. A review on diabetes and atherosclerosis showed that the metabolic abnormalities due to diabetes predispose to vascular changes, which in turn lead to atherosclerotic end-points.[28] Very high risk for CAD among diabetic subjects lead the American Diabetic Association to label diabetes as a ***cardiovascular risk equivalent.***[30]

In the CUPS study the percentage of death was significantly higher among diabetic subjects (17/143, 11.9%) compared to non-diabetic subjects (33/997, 3.3% $p<0.001$). The American Heart Association has recently stated that ***"Diabetes is a cardiovascular disease."***[31]

Cardiovascular disease accounts for 70-75% of deaths in Diabetic people, with acute myocardial infarction being responsible for 30%.[32] A two to four fold excess in mortality due to CAD among individuals with diabetes has been noted in a number of prospective studies encompassing a variety of ethnic and racial groups.[33]

In the study by Jackson[34] et al, the prevalence of major CAD is increased from 9.0% in subjects with normal glucose tolerance to 17% in those with impaired glucose tolerance and 20% in diabetes. Similarly the famous study of ***Clawson and Bell***[35] of approximately 1200 diabetics and 50,000 non diabetic control shows that total CAD in diabetics was between 2 and 10 times greater than in

control. Increased severity is indicated by a greater number of affected vessel in an individual patient i.e higher incidence of double and triple vessel disease, increased extent of disease is evidenced by the longer individual lesions. In addition diabetics show an increased incidence of combined proximal and distal disease i.e more diffuse CAD. Finally IHD developed at a younger age in diabetics as compared to non diabetics.[36]

The WHO multinational study[37] on vascular disease in diabetics numbering 4740 and aged 35-55 years found that all cause mortality in diabetics was increased three fold for male and four fold for female diabetic patients as compared to non-diabetics. Among various ethnic populations, south Asians including Indian have a high prevalence of NIDDM and a high incidence of IHD. Wood et al,[38] confirmed that the relative risk of AMI due to DM was 3.3 in Asians but only 1.3 in Europeans and that clinical DM account for 21% of Myocardial infarction in Asians but only 3% of myocardial infarction in Europeans. They concluded that diabetes alone can account for the whole of excess deaths from IHD among Asians in the U.K. without the need to incorporate smoking, Hypertension, or Dyslipidemia. The mechanism behind the higher morality are unclear but contributing factors could include co-existing diabetic cardiomyopathy, Autonomic neuropathy, the adverse cardiac and metabolic effects of non essential fatty acids

levels and increased susceptibility to ischemic damage because of a reduced ability to maintain high glycolytic rates during ischemia.[39] This conclusion that an underlying cardiac abnormality exists in diabetics, in addition to CAD, is based on the finding of a greater number of abnormalities of left ventricle systolic function and segmented wall motion and a higher incidence of recurrent myocardial infarction, cardiogenic shock, CCF, conduction disturbance and myocardial rupture.[40]

SILENT MYOCARDIAL ISCHEMIA

Silent myocardial ischemia is defined as presence of objective evidence of myocardial ischemia in the absence of Angina or equivalent symptoms.[41]

The incidence of painless ST segment depression during exercise stress test in diabetic patients is more than double when compared to non-diabetic subjects 75% Vs 35%.[42] The propensity of patients with diabetes to present with either silent or unrecognized myocardial infarction is well established.[32]

Koistinen et al,[43] studied the prevalence of asymptomatic myocardial ischemia in diabetic subjects and found high prevalence of asymptomatic myocardial ischemia in diabetics 29% Vs 5% in

non-diabetic. Certain notable difference have been observed regarding the clinical features and diagnosis of IHD in diabetics.[36]

1. The symptoms of Angina may be masked in diabetic patients leading to silent myocardial ischemia and myocardial infarction.

2. Atypical anginal symptoms including symptoms of CCF are more common in diabetes.

3. CAD is not well predicted by resting ECG abnormalities.

Silent myocardial ischemia occurs more frequently in diabetic patients with autonomic neuropathy perhaps due to involvement of sensory innervations of heart.[44] A heightened somatic pain threshold possibly due to peripheral neuropathy may also blunt the perception of Angina in some diabetic subjects.[45]

Rangadayalan et al,[46] speculated that silent myocardial ischemia and decreased perception of Angina could be hazardous as they deprive patients warning sign thereby allowing ischemia to intensity further. More over studies have shown presence of myocardial scar in the absence of antemortem history of myocardial infarction which is three times more frequent in diabetic patient than in those without diabetes.[47]

METHODS TO DETECT SILENT MYOCARDIAL ISCHEMIA

1. Positive Exercise test in an asymptomatic high risk individual.

2. Transient ST segment elevation in Random (or) Ambulatory electrocardiography.

3. Transient LV motion abnormality at rest or during stress in echocardiography.

4. Transient perfusion defect on Thallium 201 scintigraphy.

TREAD MILL TEST

Paillole et al,[48] designated a study to determine the sensitivity and specificity of three non invasive tests viz., 48 hours Ambulatory ECG monitoring, Maximal ECG exercise test and intravenous dipyridamole Thallium Scintigraphy (DMTS). This study proved that as the exercise test is cheaper and more widely available than the DMTS, it should be used as a first line examination. DMTS may provide an alternative solution for those patient who can not perform maximal exercise or those with a typical clinical presentation. Now TMT is most frequently used to estimate prognosis and to determine the likelihood and extent of CAD, the patients functional capacity and the effect of therapy. A number of studies has shown that, in TMT positive patients, 76% of patients

have coronary stenosis of 50% or greater on Angiography and are **true positive.** The rest 24% are labeled as **false positive.** In TMT negative patients angiography showed 38% are **false negative.** Females have high false positive 54% Vs male 17%.[49]

The predictive value of positive test may be further enhanced by considering of not only ST segment response but also exercise time, workload, BP response, Heart rate response.[50]

The treadmill protocol should be consistent, with the patient's physical capacity and the purpose of the test. In healthy individuals the standard "Bruce" protocol is popular and large diagnostic and prognostic data base has been published using this protocol.[51]

The Bruce multistage maximal treadmill protocol has 3 minute periods to allow achievement of a steady state before workload is increased. In older individuals (or) those whose exercise capacity is limited by cardiac disease, the protocol can be modified by two 3 minutes warming up stages at 1.7 miles per hour and with 0 percent grade and 1.7 miles per hour and 5% grade.

PRINCIPLES OF EXECISE ELECTRO CARDIOGRAPHY

The principle of exercise testing is the measurement of capacity of the coronary circulation to augment coronary blood flow in response to increase oxygen demand because the heart rate at

resting work load extract almost all of the available oxygen 75 to 80%, increased cardiac work require an increase in blood flow which is commensurable with the work. An increase in the cardiac output is accomplished in large part by a increase in heart rate. There is a linear relationship and one can reliably be estimated from the other. Therefore when a subject increases his heart rate from the basal state to an age related maximum, we can predict that his heart has reached its maximum cardiac output and has increased coronary blood flow as much as possible. When the coronary circulation is unable to augment during exercise such as in CAD, It manifests as familiar ST segment depression in the ECG.

EXERCISE PHYSIOLOGY DURING TREADMILL TEST

Cardiac output increases 4-6 folds above basal levels during strenuous exertion in the upright position, depending on genetic environment and level of training. The maximum heart rate (MHR) can be estimated from the formula.[51]

MHR = 220 – age in years (with standard deviation of 12 beats/min).

The age predicted maximum heart rate is useful measurement for safety reasons.

In post exercise phase, hemodynamics returns to baseline within minutes of termination of exercise. Vagal reactivation is an important cardiac deceleration mechanism after exercise and the acceleration is well in trained athletes but blunted in patients with chronic heart failure.[51]

The work done during the treadmill test is expressed in metabolic equivalents (MET) which refer to unit of oxygen uptake in a sitting, resting person. One MET is equivalent to 3.5 ml O2/kg/min of body weight.[51]

MET's ASSOCIATES WITH ACTIVITY

Work activities can be calculated in multiples of METS. The measurements obtained with cardiopulmonary exercise testing are useful in understanding an individual patient response to exercise and can be useful in the diagnosis and evaluation of a patient with dyspnoea.[51]

TYPES OF ST SEGMENT DISPLACEMENT IN TREADMILL

In normal persons the PR, QRS and QT intervals shorten as heart rate increases – 'P' amplitude increases and the PR segment becomes progressively more down sloping in the inferior leads.

'J' (Junctional) point depression is a normal finding during exercise. In patients with myocardial ischemia, however the ST segment usually becomes more horizontal as the severity of the ischemic response worsens. With progressive exercise the depth of the ST segment depression may increase, involving more ECG leads and the patient may develop angina.[51]

In the immediate post recovery part the ST segment displacement may persist with down slopping ST segment and 'T' wave inversion, gradually returning to baseline after 5-10 minutes. In about 10% of patients the ischemic response may appear only in the recovery phase.

The eight different ECG patterns seen during exercise testing:

1. The normal and rapid upsloping ST segment response are normal response to exercise.

2. J Point depression with rapid upsloping ST segments is a common response in an older, apparently healthy population.

3. Minor ST depression can occur occasionally at sub maximal workloads in patients with CAD in this illustration, the ST segment is depressed 0.09 mV (0.9 mm) 80 m sec after the J point.

4. The slow upsloping ST segment pattern often demonstrates an ischemic response in patients with known coronary disease or those with a high pretest clinical risk of coronary disease. Criteria for slow upsloping ST segment depression include J point and ST 80 depression of 0.15 mV or more and ST segment slope of more than 1.0 mV/sec.

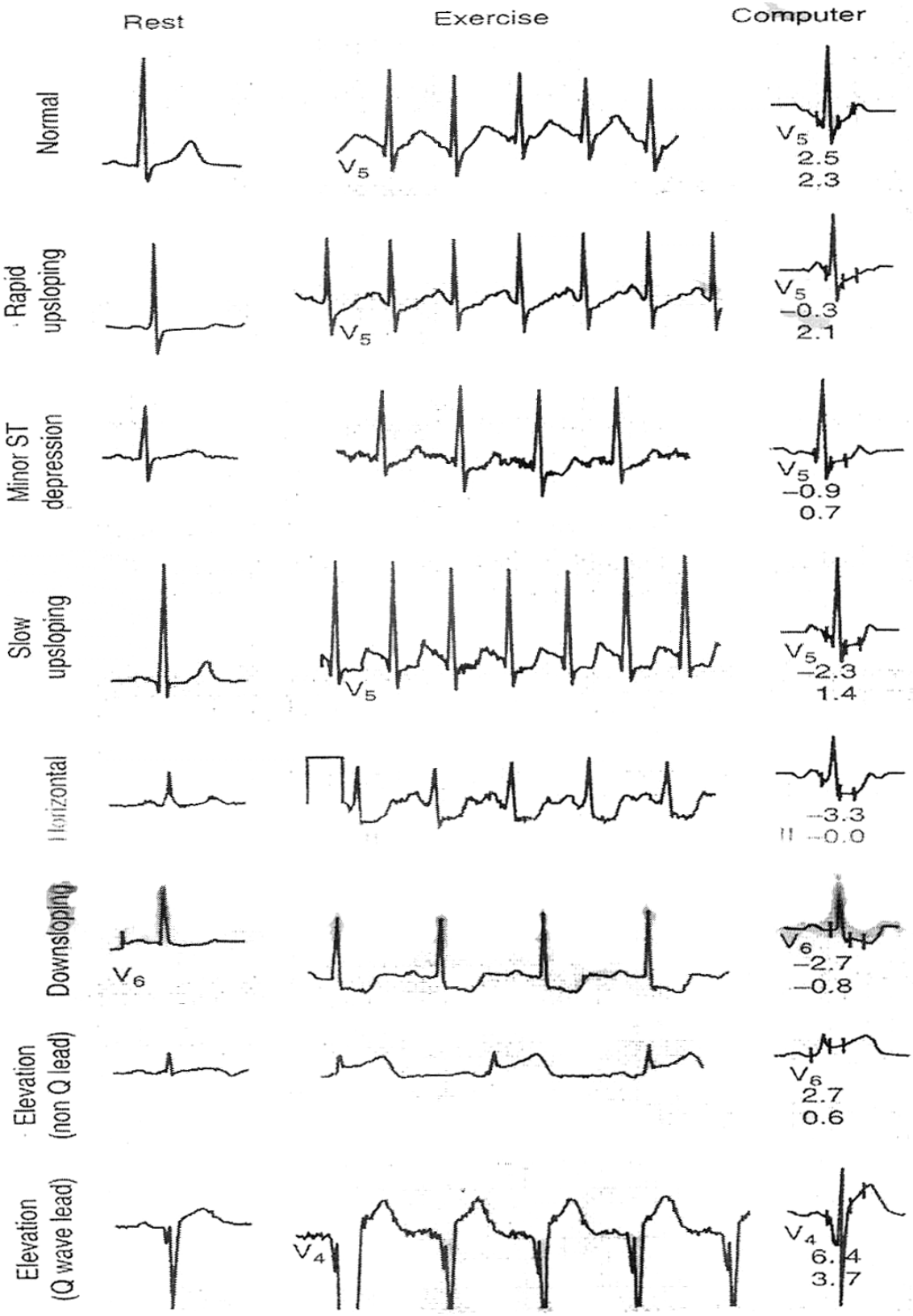
5. Classic criteria for myocardial ischemia include horizontal ST segment depression observed when both the J point and ST 80 depression are 0.1 mV or more and ST segment slope is within the range of 0.1 mV/sec.

6. Down sloping ST segment depression occurs when the J point and ST 80 depression are 0.1 mV and ST segment slope is -1.0 mV/sec.

7. ST segment elevation in a non Q wave non infarct lead occurs when the J point and ST 60 are 1.0 mV or greater and represents a severe ischemic response.

8. ST segment elevation in an infract territory (Q wave lead) indicates a severe wall motion abnormality and in most cases is not considered as ischemic response.

TYPES OF ST SEGMENT DISPLACEMENT IN TREADMILL



NON CORONARY CAUSES OF ST SEGMENT DEPRESSION[51]

1. Severe aortic stenosis	9. Glucose Load
2. Severe hypertension	10. Left ventricular hypertrophy
3. Cardiomyopathy	11. Hyperventilation
4. Anemia	12. Mitral valve prolapse
5. Hypokalemia	13.Intraventricular conduction disturbance
6. Severe hypoxia	14. Preexcitation syndrome
7. Digitalis use	15. Severe volume overload (aortic, mitral regurgitation)
8. Sudden excessive exercise	16. Supraventricular tachyarrhythmias

Exercise Parameters Associated with an Adverse Prognosis and Multivessel Coronary Artery Disease[51]

1. Duration of Symptom-limiting exercise <5 METs
2. Failure to increase systolic blood pressure ≥ 120mm Hg, or a sustained decrease ≥ 10mm Hg, or below rest levels, during progressive exercise.
3. ST segment depression ≥ 2mm, down sloping ST segment, starting at < 5 METs, involving ≥ 5 min into recovery.
4. Exercise-induced ST segment elevation (a VR excluded)
5. Angina pectoris at low exercise workloads
6. Reproducible sustained (> 30 sec) or symptomatic ventricular tachycardia
7. Acute systemic illness (pulmonary embolism, aortic dissection)

MEASUREMENT OF ST SEGMENT DISPLACEMENT

For purpose of interpretation, the PQ junction is usually chosen as the iso electric point. The TP segment represents a true iso electric point but is an impractical choice for most routine clinical measurements. The development of 0.1 mV (or) greater of 'J' point depression measurement from the PQ junction with a relatively flat ST segment slope (e.g. < 0.7 to 1 MV /sec), depressed 0.10 MV (or) more 80 m.sec after the 'J' point (ST 80) in three consecutive beats with a stable baseline is considered to be an abnormal response.[51]

When the ST 80 measurement is difficult to determine at rapid heart rate (> 130 beats/min) the ST 60 measurement should be used. The ST segment at rest may occasionally be depressed. When this occurring the 'J' point and ST 60 (or) ST 80 measurement should be depressed an additional 0.1 MV (or) greater to be considered abnormal.[51]

When the degree of resting ST depression is 0.1 MV (or) greater, the exercise ECG becomes less specific and myocardial imaging modalities should be considered. Exercise induced ST segment depression does not localize the site of myocardial ischemia nor does it provide a clue about which coronary artery involved. But exercise induced ST segment elevation is relatively specific for the territory of myocardial ischemia and coronary artery involved.[51]

MECHANISM OF ST SEGMENT DEPRESSION

Dynamic changes in coronary artery at the site of an atherosclerotic plaque may result in diminished coronary flow during static (or) dynamic exercise, instead of the expected that normally occur from coronary vasodilatation in a normal vessel; that is perfusion present distal to the stenotic plaque actually falls during exercise, resulting in reduced subendocardial blood flow. Thus regional left ventricular myocardial ischemia may result not only from an increase in myocardial oxygen demand during exercise but also from a limitation of coronary flow as a result of coronary vasoconstriction (or) inability of vessels to sufficiently vasodilate at (or) near the site of an atherosclerotic plaque.[51]

In normal persons, the action potential duration of the endocardial region is longer than that of the epicardial region and ventricular repolarisation is from epicardium to endocardium. The action potential duration is shortened in the presence of myocardial ischemia and electrical gradients are created, resulting in ST segment depression (or) elevation depending on the surface ECG leads. At the molecular levels, activation of sarcolemmal ATP – sensitive potassium channels by ischemia ATP depletion may play a role.

NON ELECTRO CARDIOGRAPHIC OBSERVATIONS IN TREAD MILL

EXERCISE CAPACITY

There appears to be no correlation between performance of maximal testing and predictive value of ST segment response. However the development of evidence of ischemia at low work load is associated relatively high risk of subsequent events.[52]

EXERCISE TIME

The importance of exercise time is evident. ST depression occurring after 6 minutes of standard Bruce protocol is associated with relative risk of 6.7, 3.6 in men and women respectively when compared to ST depression occurring within 5 minutes associated with relative risk of 14.7, 5.6 in men and women respectively.[53]

BLOOD PRESSURE

Perhaps the most important parameter to be monitored closely is blood pressure for patient safety and also for its diagnostic contribution. The normal exercise response is to increase systolic BP progressively with increasing work loads to a peak response ranging from 160-200 mmHg with the higher range of the scale in older patients with less compliant vascular system. In asymptomatic

normotensive individuals an exaggerated exercise systolic BP to 214 mmHg (or) greater (or) an elevated systolic (or) diastolic BP at the 3rd minute of recovery is associated with significant increased long term risk of hypertension.[51]

If blood pressure fails to increase with increasing work load (or) drops at less than maximal work load, this can be a strong predictor of CAD.[51]

HEART RATE RESPONSE

The magnitude of heart rate response is related to cardiac reserve, the state of physical fitness and is dependant on interplay between sympathetic and parasympathetic nervous system. Blunted heart rate response to Exercise termed as ***chronotrophic incompetence*** increases the risk of future coronary event in Diabetes.[54]

As stated by ***Borlow*** irrespective of age, gender and risk factors, exercise ***stress testing remains a most practicable and cost effective method for detecting CAD.*** This should not be judged unreliable because of high prevalence of false positive results.[55]

ATHEROTHROMBOTIC DISEASE

Several risk factors have been identified for CAD in General population. RISK FACTORS ARE.

I PREDISPOSING FACTORS

1. Age
2. Sex
3. Family History
4. Genes

II RISK MODIFYING BEHAVIOURS

1. Smoking
2. Athero genic diet
3. High Alchocol consumption
4. Physical activity

III METABOLIC RISK FACTORS

1. Dyslipidemia

2. Hypertension

3. Obesity

4. Diabetes mellitus

5. Metabolic Syndrome

IV DISEASE MARKERS

1. Calcium Score

2. Catheterization result

3. Stress test results

4. Left Ventricular Hypertrophy

5. Previous History of Myocardial Infarction

6. Inflammatory State

SMOKING

The effect of smoking by a diabetic is to double or Triple the already increased risk of IHD and also increase CAD mortality by 50%. Chronic cigarette smokers are insulin resistant, hyper insulinemic and dyslipidemic [51]

FAMILY HISTORY OF DIABETES AND IHD

Strong Familial aggregation of the disease has been noted in Indians and also in other Asian populations. In India nearly 75% of the Type 2 Diabetic patients have first degree family history of Diabetes. The risk of the offspring developing diabetes with a parental history increases above 50% and it is around 40% if the proband has the diabetic sibling.[56,57] Family history of IHD is an important independent risk factor for CAD in General population.

PHYSICAL INACTIVITY AND SEDENTARY OCCUPATION

The impact of physical inactivity is manifested more markedly in populations which had been accustomed to habitual heavy physical activity. Migration from rural areas to urban slums in metropolitan cities leads to obesity, glucose intolerance and dyslipidemia.[58,59] The risk of developing diabetes and CAD was more in subjects who followed a sedentary lifestyle.[60]

METABOLIC SYNDROME

Clustering of multiple cardiovascular risk factors has been known for at least 80 years. Kylin initially reported that hypertension, hyperglycemia and high uric acid levels in the same individual predicted increased risk of coronary heart disease.[61] Insulin resistance in diabetes was reported by Himsworth in 1939 in a series of Goulstonian Lectures to the Royal College of Physicians in London. He challenged the conventional wisdom that all diabetes was caused by lack of insulin and demonstrated that "a state of diabetes may result form inefficient action of insulin as well as deficiency of insulin"[62]

Insulin resistance syndrome as a single disease entity was reported in 1988 by Reaven who reported clustering of multiple abnormalities of glucose and lipid metabolism and called it syndrome X or insulin resistance syndrome.[63] He included insulin resistance, hyperglycemia, hypertension, low HDL cholesterol and high VLDL triglycerides. He surprisingly missed obesity or visceral obesity from the definition which was later added as a crucial abnormality. Various names were subsequently proposed the latest being the metabolic syndrome.[61] The cause of the metabolic syndrome remains obscure. Reaven proposed that ***insulin resistance*** was the most important abonormality.[64]

METABOLIC SYNDROME - A PREDICTOR OF CARDIOVASCULAR DISEASE

The relation of insulin resistance to cardiovascular risk, particularly to coronary artery disease (CAD) has been well established in many prospective studies in the West. In 1,209 Finish men aged 42-60 years, the 10-year CVD risk was increased 2.1-and 2.5-fold with the ATPIII and WHO metabolic syndrome definition, respectively.[64] The metabolic syndrome alone predicted ~ 25% of all new-onset CVD mortality by 1.2-2.8 times.[65]

PREVALANCE OF METABOLIC SYNDROME IN INDIA

A recent population based study in south Indians compared prevalence of metabolic syndrome using WHO, ATP III and IDF definitions, the prevalence of metabolic syndrome were 23.2% 18.3% and 25.8% respectively.[52]

PATHOGENESIS OF ATHEROSLEROSIS IN DIABETICS

ROLE OF HYPERGLYCEMIA

Cardiovascular risk rises as blood glucose increases above subdiabetic levels. The relationship may be J-shaped. In diabetic people, tight glycemic control has not yet been shown to reduce macrovascular events, except of metformin treatment, which

significantly decreased fatal myocardial infarction rate in type 2 diabetic patients. Other actions of metformin (reducing pressure and obesity) may be responsible.[66]

Hyperglycemia leads to advanced glycation end-products (AGE) formation in the arterial wall, damaging structural proteins and generating toxic reactive oxygen species. Sequelae include increased endothelial permeability, impaired nitrous oxide (NO) mediated vasorelaxation, upregulation of procoagulant and adhesion proteins on the endothelium and attraction of macrophages that form foam cells. AGEs interact with specific receptors (RAGEs) on endothelial and other cells to cause specific effects. Genetic polymorphisms of the RAGE gene may modulate production of inflammatory mediators in arteries. Insulin stimulates vascular smooth muscle cell proliferation and production of the fibrinolysis inhibitor, plasminogen activator inhibitor (PAI). High insulin levels in insulin resistant states may therefore be atherogenic. Other commonly associated risk factors are hypertension (30-40% of diabetic people), dyslipidemia - typically normal low dentsity lipoproteins, dominated by highly atherogenic small dense low-density lipoprotein, low high-density lipoproteins, raised triglycerides and obesity, an independent risk factor.[66]

DYSLIPIDEMIA IN TYPE 2 DIABETES MELLITUS

Lipid metabolism is commonly disarranged by diabetes mellitus, often with additional contributions from coexistent renal or hepatic disorders. These lipid alterations play an important role in the development of atherosclerosis and contribute to the instability of atheromatous plaques. Gross hypercholesterolemia but at any given level of cholesterol, a diabetic subject has two to three times the cardiovascular risk of non-diabetic.[66]

Lipid abnormalities associated with type 1 diabetes are largely related to the level of glycemic control. Hyperglycemia is associated with raised low-density lipoprotein (LDL) cholesterol and triglyceride concentrations and low HDL-cholesterol abnormalities which are reversed by normalizing glycemia.[66]

The pattern of dyslipidemia in type 2 diabetes is that characteristically seen in the insulin-resistant states and the metabolic syndrome. Low HDL and raised triglyceride concentrations are accompanied by normal LDL-cholesterol levels, although this is likely to be dominated by highly atherogenic small dense LDL particles. Non-diabetic but insulin resistant first degree relatives of type 2 diabetic subjects share this atherogenic profile, suggesting that it precedes the development of clinical diabetes.[66]

SYSTEMIC HYPERTENSION

Hypertension commonly coexists with type 1 and type 2 diabetes and is particularly associated with diabetic nephropathy. In its own right, it is a major risk factor for both myocardial infarction and stroke. In the UKPDS, 32% of type 2 diabetic males and 45% of females with no clinical evidence of atheromatous disease were hypertensive (according to the World Health Organization criteria of systolic pressure> 160 mmHg and / or diastolic > 90 mm Hg) or were taking antihypertensive drugs. In male subjects who already had coronary artery disease, the prevalence of hypertension was even higher at 46%.[66]

Hypertension is an important feature of the cluster of cardiovascular risk factors termed the metabolic syndrome. The links between these factors remain largely unexplained. The characteristic dyslipidemia of insulin resistance may contribute to hypertension, as small dense LDL particles are especially susceptible to oxidation and oxidized LDL can suppress endothelial NO production and so promote vascoconstriction; hypertriglyceridemia also impairs endothelium dependent vasorelaxation. A role of dyslipidemia is supported by studies showing that fibrates used to treat hypercholesteroleamia also reduced the prevalence of hypertension by up to 25%.[66]

OBESITY

Obesity predisposes to type 2 diabetes, hypertension, dyslipidaemia and ultimately atheroma – one of the major causes of premature death in the obese. Indeed, obesity is now recognized as a cardiovascular risk factor in its own right.[66]

Truncal or male-pattern obesity, with excess fat deposited both subcutaneously around the abdomen and within the visceral cavity is particularly associated with type 2 diabetes and the other components of the metabolic syndrome. For unknown reasons, truncal obesity is associated with insulin resistance and proinflammatory responses that cause glucose intolerance and a highly atherogenic risk profile. Candidate mediators produced by adipose tissue that may contribute include NEFAs and cytokines such as TNF-alpha. Reduced levels of adiponectin, an insulin sensitizing protein whose secretion by adipose tissue is paradoxically decreased in obesity, may also contribute to both insulin resistance and atherogenesis. The thiazolidinediones ameliorate some of these adverse effects of adipose tissue (e.g. lowering NEFA levels), raising the prospect that these agents may reduce cardiovascular risk in Type 2 Diabetes.[66]

HAEMOSTASIS IN DIABETES

Diabetes is associated with a variety of abnormalities in coagulation, fibrinolysis and platelet function. These include increase in specific procoagulant proteins – factor VIII, vWF, factor VII, factor X and fibrinogen together with decrease in coagulation inhibitor proteins and antithrombin III. Some of these disturbances differ quantitatively between type 1 and type 2 diabetes and some show particularly strong associations with atherothrombotic disease and with microvascular complications, especially nephropathy.[66]

ATHERO THROMBOTIC DISEASE

Atheroma develops earlier and faster in diabetes, leading to widespread lesions throughout the arterial tree, including the smaller arteries. Thickening of the intima is an early change. Hyaline degeneration and thickening of the muscular media may contribute to hypertension and often undergoes calcification (medial sclerosis). An important functional abnormality is impaired arterial relaxation, due to failure of the endothelium to produce nitrous oxide (NO), a potent vasodilator. Procoagulant changes on the endothelial surface promote adhesion of macrophages (the precursors of foam cells of the atheromatous plaque) and platelets, favoring thrombosis. Platelet rich thrombus in the coronary arteries is unstable and likely to rupture, causing acute coronary occlusion.[66]

CLINICAL SYNDROMES AND MANAGEMENT

Myocardial ischemia may present atypically or without pain and 'silent' ischemia carries a worse prognosis than in non-diabetic people. Typical symptoms such as dyspnoea, fatigue, or nausea and vomiting were the presenting complaint in DM with MI in 32-42% compared with 6-15% in non DM with MI.[32] Vascular disease in the legs and cerebral circulation commonly coexist and are two to three times more frequent than in the general population. Early and extensive investigation (including invasive test such as coronary angiography) may therefore be needed in patients with few symptoms.[66]

Primary preventative measures includes weight loss if obese, regular physical activity and smoking cessation; optimizing glycemic control, using metformin in obese type 2 patients; correcting dyslipidemia and hypertension; and aspirin (75 mg / day). Target cholesterol concentration is <4.8 mmol/L and blood pressure should be <135/85 mmHg.[66]

Beta blockers and angiotensin-converting enzyme (ACE) inhibitors are useful in treating angina and hypertension and also have cardioprotective effects in diabetic patients. ACE inhibitors also slow the progression of nephropathy and some calcium channel antagonists decrease the risk of infarction in diabetic people. Heart

failure is treated conventionally with ACE inhibitors and diuretics; certain beta blockers (e.g. carvedilol) may also be useful.[66]

Unstable angina carries a 50% higher risk of progression to myocardial infarction than in non-diabetic subjects and requires intensive treatment with low molecular-weight heparin and a beta blocker; addition of either clopidogrel or a platelet glycoprotein inhibitor further reduces risk of infarction or death. Urgent coronary revascularization is indicated if medical measures fail.[66]

Acute myocardial infarction should be treated with immediate thrombolysis (even in the presence of retinopathy), aspirin and a cardioselective beta-blocker. An ACE inhibitor should be given early unless contraindicated. Blood glucose should be tightly controlled in all diabetic patients, according to the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) protocol, insulin / glucose solution infused intravenously to maintain levels of 7-11 mmol/L for at least 24 hours, followed by intensive subcutaneous insulin treatment for at least 3 months. Insulin given in this way may reduce myocardium from non-esterified fatty acids and block excessive neuroendocrine activation.[66]

Coronary revascularization relieves symptoms as effectively in diabetic as in non-diabetic people, although long-term survival is lower. Percutaneous transluminal coronary angioplasty (PTCA) with

stenting (and probably a platelet inhibitor) is preferred for accessible lesions in larger vessels. Coronary artery bypass grafting (CABG) is generally reserved for difficult or multiple occlusions and for re-stenosis after angioplasty.[66]

MATERIALS AND METHODS

PLACE OF STUDY:

Government Kilpauk Medical College Hospital, Chennai-10.

DURATION OF STUDY: July 2006 to June 2007

INCLUSION CRITERIA:

1. Newly detected Type 2 DM – Patients detected Type-2 diabetes recently within 6 months duration.

   Patients diagnosed to have DM on full filling any one of the following criteria devised by ADA Recommendation.

   1. Fasting plasma glucose ≥ 126mg%
   2. Post prandial plasma glucose ≥ 200 mg%
   3. Symptoms of diabetes with Random plasma glucose ≥ 200 mg %.

2. Known Type 2 Diabetic patients of various duration on treatment.

3. Age between 30 and 60 years.

4. Patients should not have any CAD symptoms.

5. Resting ECG, X-ray chest and Echocardiography should be normal.

EXCLUSION CRITERIA

1. Type 1 Diabetes Mellitus.

2. Known case of CAD.

3. Signs of left ventricular failure.

4. Patients with peripheral vascular disease as evidenced by absent peripheral pulses.

5. Patients without microvascular complication.

   (i) Retinopathy excluded by fundus examination.

   (ii) Albimunuria by dispstic method.

   (iii) Autonomic neuropathy.

6. Uncontrolled Systemic hypertension.

7. Age less than 30 years and more than 65 years.

8. Other absolute contraindications for exercise stress test.

STUDY POPULATION

Of the 205 patients enrolled for the study who attended out patient department of Government Kilpauk Medical College Hospital, 40 Patients of type 2 DM were selected for Treadmill test. Rest of the patients excluded as per exclusion criteria. 20 non diabetic patients also selected as control. Tread mill test was performed for these 60 patients using standard bruce protocol.

STUDY DESIGN

Case – Control Study

LABORATORY METHODS

Fasting plasma glucose was measured overnight fasting sample and 2 hour post prandial glucose measured from the sample taken 2 hours after routine break fast by semi autoanalyser using glucose oxidase and pyruvate oxidase method.

For lipid profile (Serum total cholesterol, HDL, TGL) after 12 hours of overnight fasting and were measured by ERBA KIT semi autoanalyser using enzymatic method. Serum LDL was calculated using

FRIEDWALD'S FORMULA

LDL = TC – HDL – TGL / 5 if total cholesterol is less than 100 mg / dl.

From the patient height and weight BMI was calculated by using the formula:

BMI = Weight in Kg / (Height in meters)^2

TREAD MILL TEST

Techniques

1. The standard Bruce protocol was used since large diagnostic and prognostic data has been published using this protocol. The bruce multistage maximal treadmill protocol has 3 minutes periods to allow achievement of steady state before work load is increased.

2. Patients were instructed not to eat or drink caffeinated beverages for 3 hours before testing and to wear comfortable shoes and loose fitting cloths.

3. Unusuals physical exertion was avoided before testing.

4. Patients were advised about the risk and benefits of the procedure.

5. A written informed consent form was obtained.

6. Adequate skin preparation was done to obtain high quality recordings.

7. The areas of electrode application are rubbed with an alcohol pad to remove oil & rubbed with free sand paper and a rough material to reduce skin resistance to 5000 ohms.

8. Cables connecting the electrodes and recorders were light flexible and properly shielded.

9. Room temperature was adjusted between 64 and 72°F (18 & 22°C) and humidity less than 60%.

10. Tread mill walking was demonstrated to the patients.

11. The heart rate, blood Pressure and ECG were recorded at the end of each stage of exercise. Immediately before & immediately after stopping exercise, at the onset of an ischemic response and for each minute for at least 5-10 minutes in the recovery phase.

12. A minimum of three leads were displayed continuously on the monitor during the test.

13. Patients were at the sitting position immediately after the exertion.

14. The supine position was avoided because it increases end diastolic volume and has the potential to augment ST segment changes.

TMT RESULTS INTERPRETATION

Normal response

In normal persons, PR, QRS and QT intervals shorten as the heart rate increases. P amplitude increases and PR segment becomes progressively more downsloping in the inferior leads. J point or junctional depression is the normal finding during exercise.

Abnormal response

The development of 0.1 mV (1 mm) or greater of J point depression measured form the PQ junction with a relatively flat ST segment slope depressed 0.1 mV or more 80 m.sec. after the J point (ST 80) in 3 consecutive beats with a stable baseline is considered to be an abnormal response. When the ST 80

measurement is difficult to determine at rapid heart rate (>130 beats/min), ST 60 measurement is used.

In our study

1. ST segment depression of ≥ 1mm during exercise and early recovery period was considered to be TMT positive for inducible ischemia.

2. Development of classical angina during the test is considered to be strongly positive response.

3. Patients who have not completed stage III and failed to achieve 85% of target hear rate, the TMT results are declared inconclusive.

Workload

Workdone during the exercise stress test is expressed in MET (Metabolic equivalents). 1 MET = 3.5 ml/O2/min/Kg of body weight.

Exercise time

Exercise time is calculated in minutes. Each stage is consisted of 3 minutes

Hypertensive Response

Hypertensive response during treadmill was considered when systolic BP more than 214 mmHg. These types of patients are more prone to develop hypertension in the future.

The TMT was terminated if the patient developed any of the following features.

1. Drop in systolic blood pressure despite an increase in workload.

2. When accompanied by other evidence of ischemia.

3. Moderate to severe angina (grade 3/4).

4. Increasing nervous system symptoms (e.g., ataxia, dizziness or near syncope).

5. Signs of poor perfusion (cyanosis or pallor).

6. Technical difficulties in monitoring ECG or systolic blood pressure.

7. Subject’s desire to stop.

8. Sustained ventricular tachycardia.

9. ST elevation (≥1.0mm) in non infarct leads without diagnostic Q waves (other than V1 or a VL).

10. Fatigue, shortness of breath, wheezing, leg cramps, or claudication.

11. Development of bundle branch block or intra ventricular conduction delay that cannot be distinguished from ventricular tachycardia.

12. Hypertensive response.

RESULTS AND OBSERVATIONS

Statistical analysis was carried out for diabetic patients (Cases) and non diabetic (Controls) after categorizing each variable. Age, Duration of Diabetics, Sex, BMI, WHR, Systemic hypertension, smoking, dyslipidemia were analysed among diabetic with TMT positive and Diabetic with TMT negative and non diabetic controls. The significance of difference in means between two groups was calculated using student 't' test and significance of difference in proportion using chi-square test. FISHER EXACT TEST was used when any one of the expected variable was less than 5 in chi-square test.

Statistical significance is taken when $P < 0.05$. Statistical analysis was carried out using standard formula. Microsoft Excel 2007 version and Number crunch statistical software (NCSS) were used for data entry and analysis.

40 Diabetic patients, ten of them newly detected Diabetic patients, rest 30 patients of known diabetes of various duration and 20 non-diabetic controls underwent Tread mill test. Tread mill test was done by standard Bruce protocol. Among 40 diabetic patients 2 patients are excluded from the study because their Treadmill test results are inconclusive.

In our study cases and controls are analysed for age, BMI, WHR, dyslipidemia, Hypertension and smoking.

Table 1: STUDY GROUP

Study Group	Number of Patients
Case	38
Control	20

Table 2: PATIENTS CHARACTERISTICS

S.No.	Case Number 38				Control Number 20			P Value
	Variable	Mean	95% of C.I.		Mean	95% of C.I.		
			LCL of Mean	UCL of Mean		LCL of Mean	UCL of Mean	
1	Age	48.39	45.70	51.07	46.4	43.10	49.69	0.35
2	BMI	25.26	24.22	26.29	23.71	22.38	25.03	0.06
3	WHR	0.80	0.77	0.83	0.76	0.74	0.79	0.07

Observation: There is no statistically significant difference noted in Age, BMI, WHR (P value is more than 0.05). However BMI and WHR are higher in Diabetic population (cases) than controls.

Table 3: LIPID PROFILE

S.No.	Case N = 38				Control N = 20			P Value
	Variable	Mean	95% of C.I.		Mean	95% of C.I.		
			LCL of Mean	UCL of Mean		LCL of Mean	UCL of Mean	
1	TC	200.81	189.28	212.34	205.65	189.40	221.89	0.61
2	TGL	151.36	129.52	173.21	141.65	127.64	155.65	0.53
3	HDL	28.63	27.40	29.86	35.85	33.87	37.82	0.00
4	LDL	141.23	129.67	152.79	136.45	121.71	151.18	0.61

In Lipid profile, there is statistically significant difference is noted in HDL with 'P' value of 0.0000. Total cholesterol (T.C.), Triglycerides (TGL) and low density Lipo proteins (LDL) do not show any statistically significant difference.

Table 4: PATIENTS CHARACTERISTICS

	Cases Number 38	**Percentage**	**Control Number 20**	**Percentage**	**P Value**
Hyper Tension	19	50	7	35	0.27
Smoking	10	26	6	30	0.08
Family History of Diabetes	23	61	6	30	0.02
Family History of IHD	6	10	1	5	0.40

Observation: There is no statistically significant difference noted regarding hypertension, smoking, family history of IHD between cases and controls.

Table 5: TMT PARAMETERS

S.No.	Case Number				Control Number			P Value
	Variable	Mean	95% of C.I.		Mean	95% of C.I.		
			LCL of Mean	UCL of Mean		LCL of Mean	UCL of Mean	
1	Exercise Time	7.39	6.82	7.97	8.82	8.12	9.52	0.0031
2	Work load in mets	9.13	8.46	9.79	10.88	9.95	11.81	0.0025
3	Percentage of Predicted Maximum Hear rate	91.18	88.27	94.09	95.15	93.23	97.06	0.06

TMT parameters like exercise duration in minutes, work load in mets and percentage of Target heart rate achieved are analysed between cases and controls.

Observation: There is a statistically significant difference noted between cases and controls in exercise duration and work load with a P value 0.0031 and 0.0025 respectively.

Diabetic patients are divided in to two groups TMT positive group and TMT negative group. These two groups are analysed. Among 38 cases 10 cases are TMT positive and 28 cases are TMT negative.

Table 6: PREVALENCE OF SILENT MYOCARDIAL ISCHEMIA IN CASES AND CONTROL

Total number of Patients	Number of TMT positive case	Percentage
Diabetic cases Number 38	10	26
Control Number 20	1	5

Observation: 26% among diabetic patients are positive for silent myocardial ischemia against 5% in control.

Table 7: PREVALENCE OF SILENT MYOCARDIAL ISCHEMIA IN MALES AND FEMALES

	Total Number of Patients	TMT Positive	Percentage
Male	21	6	29
Female	17	4	24

Observation: 29% of males and 24% of females are TMT positive. The 'P' value is 1.00 that is prevalence is almost equal in both sexes.

Table 8: PREVALENCE OF SILENT MYOCARDIAL ISCHEMIA WITH RESPECT TO DURATION OF DIABETES

Duration of Diabetics	No. of Patients	TMT positive	Percentage
Newly Detected	10	1	10
7 months to 5 years	9	2	22
6 to 10 years	10	3	30
More than 10 years	9	4	44

Observation: Prevalence in newly detected Type 2 Diabetes is 10%. As the duration increase the prevalence also increase from 10% in newly detected to 22% of type 2 diabetic patients with 7 months to 5 years duration, 30% in patients with 6-10 years duration and 44% in patients with more than 10 years duration.

Table 9: PATIENT CHARACTERISTICS

S.No.	TMT Positive Number 10				TMT Negative Number 28			P Value
	Variable	Mean	95% of C.I.		Mean	95% of C.I.		
			LCL of Mean	UCL of Mean		LCL of Mean	UCL of Mean	
1	Age	52.4	46.97	57.82	46.96	43.85	50.07	0.07
2	BMI	26.22	24.30	28.13	24.92	23.65	26.18	0.26
3	WHR	0.80	0.74	0.86	0.80	0.77	0.84	0.94
4	Age of onset of diabetes	40.8	33.38	48.21	41.96	38.36	45.56	0.74
5	Duration of Diabetes	10.5	3.29	17.7	5	3.03	6.98	0.031

Observation: There is a statistically significant difference exists between TMT positive group and TMT negative group regarding duration of diabetes. Age, BMI, WHR, age of onset of diabetes does not show any difference.

Table 10: LIPID PROFILE

S.No.	TMT Positive Number 10				TMT Negative Number 28			P Value
	Variable	Mean	95% of C.I.		Mean	95% of C.I.		
			LCL of Mean	UCL of Mean		LCL of Mean	UCL of Mean	
1	TC	200	174.57	227.02	200.82	187.17	214.46	0.99
2	TGL	169.3	113.25	225.34	144.96	120.92	169.00	0.39
3	HDL	26.9	24.11	29.68	29.25	27.87	30.42	0.08
4	LDL	137.7	111.77	163.62	142.5	128.79	156.21	0.71

Observation: There is no statistically significant difference in Lipid profile between TMT positive and TMT negative group.

Table 11: ANALYSIS OF RISK FACTORS-HYPERTENSION, SMOKING, FAMILY HISTORY OF IHD BETWEEN TMT POSITIVE AND TMT NEGATIVE GROUP

Risk Factors	TMT Positive Number 10	Percentage	TMT Negative Number 28	Percentage	P value
Hyper tension	8	80	11	39	0.02
Smoking	5	50	15	18	0.04
Family History of IHD	3	30	3	11	0.31

Observation: There is statistically significant difference noted in Hypertension and smoking with a P value of 0.027 and 0.047 respectively between TMT positive and TMT negative groups.

Table 12: TMT PARAMETERS

S.No.	TMT Positive Number 10				TMT Negative Number 28			P Value
	Variable	Mean	95% of C.I.		Mean	95% of C.I.		
			LCL of Mean	UCL of Mean		LCL of Mean	UCL of Mean	
1	Exercise time	6.40	5.45	7.85	7.75	7.06	8.44	0.03
2	Work load in mets	8.31	7.32	9.29	9.42	8.58	10.25	0.13
3	% Predicted Maximum H.R.	94.8	89.54	100.05	89.89	86.36	93.42	0.13

Observation: There is a statistical significant difference noted in exercise time with a P value of 0.035 between TMT positive and TMT negative groups.

DISCUSSION

In our study the prevalence of silent myocardial ischemia is 26% in Diabetics and 5% in controls. This shows silent myocardial ischemia is more common in Diabetics than non-diabetics (26% Vs 5%). In various international studies the prevalence of silent myocardial ischemia varies between 10-77%. The DIAD study[67] which is the first large prospective study in asymptomatic patients with diabetes revealed a prevalence of silent myocardial ischemia of 22%. In the study done by Koistinen et al,[43] the prevalence of SMI is 29%. In another study conducted at Department of Medicine, cardiology division, New York Medical College, New York, USA,[68] the Prevalence of SMI in Type 2 diabetics is 29%. Our study result exactly matches with these studies.

In one study conducted in Department of Cardiology, central railway head quarter hospital Byculla, Bombay, the prevalence of SMI is 38%. In another study done at Department of cardiology, All India Institute of Medical Science New Delhi,[69] the prevalence of SMI is 50% by Treadmill test and 35% on ambulatory electrocardiography.

In our study the prevalence of SMI in newly detected Type 2 Diabetes is 10%. As the duration increases, the prevalence also increases from 10% in newly detected to 22% in patients with

7 months to 5 years duration, 30% in patients of 6-10 years duration and 44% in patients with more than 10 years duration. Many studies have demonstrated the impaired glucose tolerance itself is a risk factor for CAD. SMI is present even in the stage of impaired glucose tolerance.

In one study done at Department of medicine, cardiology Division, New York Medical College, Val Halla, New York[70] and another study by Jackson et al,[34] have demonstrated SMI is present at the stage of impaired glucose tolerance itself and the prevalence increases with duration and the level of glycemic control.

In our study the prevalence of Hypertension among diabetic is 50%. The prevalence of Hypertension in TMT positive is 80% and TMT negative group is 39% with a 'P' value 0.027. Kannel WB[71] and Stamler J[72] have demonstrated that Hypertension increases the risk of CAD by two fold. In our study also, Hypertension has increased two fold risk.

Smoking is at least as prevalent among diabetic people as in general population and CAD already more common in Diabetic is even more prevalent in those who smoke.[66] In our study 26% of Diabetic and 30% of non diabetic are smokers, ie. ***both smoke equally.*** But in TMT positive group, prevalence of smoking is 50%

and in TMT negative group is 18% with a P value of 0.047. This shows that smoking increases the risk more than two fold.

Type 2 diabetes show the characteristic Lipid Profile of normal or only slightly raised cholesterol, with low HDL cholesterol and mildly elevated triglyceride concentrations.[73,74,75] In our study also total cholesterol is almost equal in both cases and controls. Triglyceride and low density lipo protein is mildly raised in Diabetic than controls but regarding HDL cholesterol, there is a significant difference between diabetic and control with a P value of 0.00. However there is no difference is noted between TMT positive and TMT negative group except for Triglycerides which is mildly increased in TMT positive (Mean: 169.3) than TMT negative group (Mean 144.96).

In our study regarding obesity, BMI and WHR are higher in Diabetics than control. (BMI Mean 25.26 Vs 23.71, WHR Mean 0.80 Vs 0.76). However there is no statistically significant difference. Similarly there is no difference in WHR between TMT positive and TMT negative group. BMI is higher in TMT positive than TMT negative group (Mean TMT positive 26.22, TMT negative 24.92). However there is no statistically significant difference.

CONCLUSION

1. The prevalence of silent myocardial ischemia is higher in diabetic when compared to non-diabetic. Silent myocardial ischemia is present in diabetic patients even at the time of detection itself.

2. As the duration of diabetes increases, the prevalence of silent myocardial ischemia also increases.

3. Though Hypertension, smoking, dyslipidemia are independent risk factor for CAD, The association of these risk factors in diabetes further amplifies the risk of CAD in diabetic patients.

4. Detection of silent myocardial ischemia-a silent disease marker which is more prevalent in diabetic can lead to the prevention of CAD which is more common, extensive and fatal in diabetes.

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